Do root canal sealers lead to cancer? How can we find out?

Nicole Gonçalves **LIMA**[1]
Mariana **TREVIZAN**[1]
Fabrício Kitazono de **CARVALHO**[2]
Paulo **NELSON-FILHO**[3]
Alberto **CONSOLARO**[4]

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ABSTRACT

Root canal sealers can be made with calcium hydroxide, zinc oxide and eugenol, glass ionomer, resin associated with methacrylate or silicone. They should be subjected to investigation on their potential for genotoxic and mutagenic effects before being launched into the specialized market, since such properties are part of the biocompatibility concept. In the present study, test modalities and the concepts of genotoxicity, mutagenicity and carcinogenesis are highlighted.

Keywords: Root canal sealing material. Micronucleus test. Comet assay. Biocompatible material.

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[1] Graduate students in Pediatric Dentistry, Universidade de São Paulo, School of Dentistry (FORP-USP), Ribeirão Preto, São Paulo, Brazil.

[2] Professor of Pediatric Dentistry, Universidade de São Paulo, School of Dentistry (FORP-USP), Ribeirão Preto, São Paulo, Brazil.

[3] Full Professor of Pediatric Dentistry, Universidade de São Paulo, School of Dentistry (FORP-USP), Ribeirão Preto, São Paulo, Brazil.

[4] Full professor of Pathology, Universidade de São Paulo, School of Dentistry (FOB-USP), Bauru, São Paulo, Brazil and Graduate Program, Universidade de São Paulo, School of Dentistry (FORP-USP), Ribeirão Preto, São Paulo, Brazil.

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Contact address: Alberto Consolaro
E-mail: consolaro@uol.com.br

Contemporary Endodontics recommends root canal filling within canal limits, with success usually being considered even if there is mild overflow of endodontic sealer, which is also known as puff.[1] Root canal sealers can be made with calcium hydroxide, zinc oxide and eugenol, glass ionomer, resin associated with methacrylate or silicone.

Although it has been acknowledged that mild sealer overflow can lead to subclinical chronic inflammatory processes or even repair processes around it, it is also known that the endodontic sealer will remain, for a long period of time, on contact with periodontal ligament cells. Thus, it seems logical to claim that if a given sealer is mutagenic, it can contribute to cause cell damage associated with neoplasms, even at a certain distance, since the periodontal ligament is highly vascularized and can carry sealer particles to other parts of the body by means of the Mononuclear Phagocyte System cells.

Biocompatibility is defined as the ability of a given material to fulfil its functions whenever applied to living tissues, without causing any damage to them. Should the material not be biocompatible with tissues, it can lead to inflammatory, allergic, mutagenic/carcinogenic reactions. The majority of studies associate dental material biocompatibility with cytotoxicity, inflammation and repair only; however, the former is also associated with mutagenesis and carcinogenesis. The absence of both mutagenesis and carcinogenesis must be a key characteristic of endodontic sealers.[10]

Genetic changes to the DNA are identified as mutations, being usually induced by errors in genetic material replication during cell division. Chemical, physical and biological substances capable of causing such changes are known as mutagenic substances, and the phenomenon or process of DNA damage induction is known as "mutagenesis."

Intense, progressive damage to the cell can cause irreversible lesion and cell death (apoptosis or necrosis), a mechanism by which the organism protects itself from permanent damage. However, under those conditions, a few cells are capable of surviving such protection mechanism, replicating in a disordered manner, thus leading to malignant neoplasm. The process of damage leading to malignant neoplasm growth results from accumulation of harmful stimuli and can be termed "carcinogenesis".[2,3]

Although it is not a carcinogenicity measure, mutagenicity is associated with cancer growth.[4] Increased DNA damage, chromosomal breakage or loss, are important factors that can induce different types of cancer to grow.[5,6] The process of carcinogenesis results from accumulation of genetic lesion/damage[7] or mutations.

The most significant cancer-related mutations occur in genes controlling cell proliferation, also known as proto-oncogenes, and tumor suppressor genes. Additionally, they result in uncontrolled growth/proliferation typical of malignant cells. Furthermore, uncontrolled genes associated with the process of DNA damage repair are also involved, particularly when they are inactive, since they can lead to mutation, thus increasing the accumulation of significant molecular changes.[8,9]

Malignant neoplasms are avoidable, and the efforts to do so focus on the identification of agents responsible for the former to occur. Taking the biocompatibility tests available into account, genotoxicity and mutagenicity assays and trials have been given special attention, since they have been generally accepted as useful indicators of carcinogenicity.[10]

Genotoxicity describes a property characterized by harmful action which damages the integrity of genetic information within a cell. Genotoxic substances can cause direct changes to the DNA or act indirectly, affecting the enzymes related to DNA replication and leading to mutations that may or may not cause cancer.[11] Nevertheless, not all genotoxic substances are necessarily mutagenic.

In genotoxicity, in order to evince cell changes, *in vitro* laboratory tests are necessary. Such tests assess, for instance, the ability of different types of material to cause damage to the DNA in cells that are compatible with those that would potentially be in contact (*in vivo*) with tissues in the human body. Human lymphocytes are a great choice, as they circulate through all tissues at all times.

Among the genotoxicity and mutagenicity assessment tests, the following are highlighted: comet assay and micronucleus test,[6] as they are highly sensitive at detecting low-level DNA changes and require a little amount of cells per sample, in addition to being versatile.[12,13] At the laboratory, the comet assay (Fig 1) assesses the potential for causing DNA

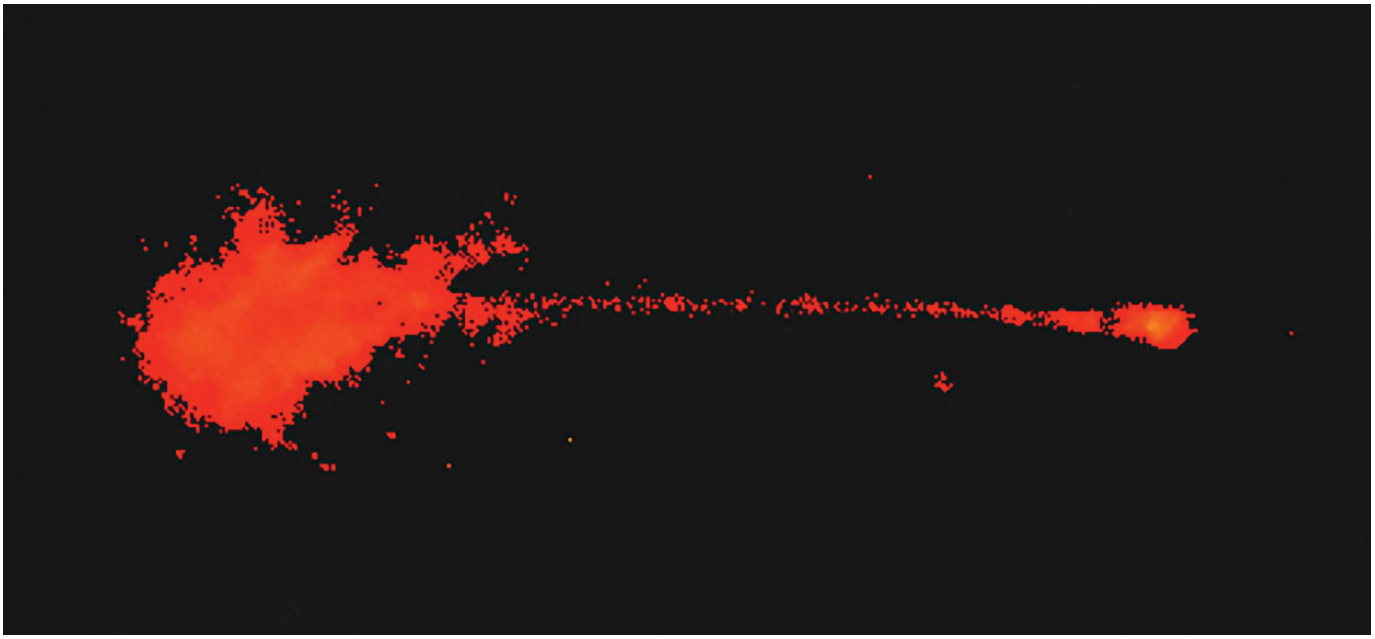

Figure 1. Comet assay showing DNA damage caused by endodontic sealer. The head accounts for the condensed DNA of considerable size, which hinders displacement. The tail accounts for the fragmented DNA which has been displaced due to electrophoresis.

lesions as a result of genotoxicity; whereas the micronucleus test assesses the potential for transferring DNA changes to daughter cells, in other words, mutagenicity.

One of the methods used for carcinogenicity assessment is the DMBA-induction experimental model in Golden Syrian hamsters for oral chemical carcinogenesis. In 1993, a study published by our research group standardized the use of the aforementioned experimental model.[14] From that point onwards, several authors have advocated the use of the model.[15-18]

Whenever choosing the endodontic sealer to be clinically used, the ideal would be to look for the product printed directions or the scientific literature to find information on the sealer's genotoxicity, mutagenicity and carcinogenicity.

Final considerations

Due to lack of studies published in the literature on the correlation between endodontic sealers and cancer, all types of dental material, especially those intended for permanent use, such as endodontic sealers, should be subjected to investigation on their potential for genotoxic and mutagenic effects[19,20] before being launched into the market.

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